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Beyond Discovery: Advances and Future Directions in Drug Repurposing Strategies a Review Article

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ABSTRACT:

A new paradigm known as "drug repurposing" or "drug repositioning" finds new therapeutic applications for licensed or novel medications outside of their initial medical indications. Due to its lower risk, faster screening times, and cost-effectiveness as compared to traditional drug discovery, which necessitates thorough preclinical and clinical testing, it has grown in popularity. Repurposed medications enable faster clinical translation and higher success rates because they already have established pharmacokinetic, safety, and toxicity characteristics. Drug repurposing has been facilitated by a variety of tactics, such as on-target and off-target methods that make use of either well-established mechanisms or recently discovered biological interactions. Large-scale data mining and drug-disease association prediction have been made possible by advances in computing technologies, particularly artificial intelligence, machine learning, network-based method, and bioinformatics, which have revolutionized repurposing. Computational simulations are validated by complementary experimental methods including genome-wide CRISPR-Cas9 research and phenotypic screening. The discovery of repurposing signals in clinical populations is further supported by real-world data sources, including electronic health records, claims databases, and multimodal datasets. Despite having benefits, there are also issues associated with drug repurposing such as restrictions on intellectual property, complicated regulations, issues with data veracity, and a dearth of common benchmarking datasets for predictive models. With an emphasis on the growing importance of AI and data-driven analytics in accelerating therapeutic innovation and solving unmet clinical needs, this study offers an overview of current approaches, techniques, applications, and constraints related to drug repurposing.

Keywords: Drug repurposing, Artificial intelligence, Machine learning, phenotypic screening, Real world data

INTRODUCTION:

Even though there is substantial progress in methodologies along with exponential growth in the money invested in research and development, drugs which are recently approved are still unchanged in number. Also, in the area of oncology, of all the drugs that enters the clinical trials at first phase, only 5% drugs get approved, which resulted in identifying extended therapeutic implications for existing drugs by a strategy called drug reprofiling. [6] The approach which involves utilization of current drugs for a different Pathological condition, which was generally not supposed to be treated the condition by this current drug is Known as drug repurposing. [1] As the methods to discover new therapeutic agents possess significant risks with higher cost and time consuming, drug reprofiling emerging as favorable and cost-effective approach to find novel therapeutic utilities for both drugs which are in current use and drugs which are in trial stages [3] and also these techniques utilized to detect any advanced agents with new therapeutic activity from currently used therapeutic agents which had been approved by FDA. [2] AI being an essential element of data science, designed to simulate and improve the cognitive abilities in humans, which includes decision making, learning and problem-solving the application of drug reprofiling with help of Al, confirmed to be economical and more efficacious when compared to Conventional experimental approaches. Modeling mediated by AI along with algorithmic methods leads to quick assessment of enormous combinatorial libraries and recognizing drugs with strong physiological actions without tiring scientific research methods. [5] Inspite of its feasibility, drug reprofiling remains restricted due to insufficient focus from pharmaceutical industries. [4] This review mainly focusses about strategies, experimental approaches for repurposing of drugs and the limitations and future directions associated with drug repurposing.

Rationale:

The rising costs, protracted timelines, and high attrition rates of traditional drug development have called for novel and sustainable approaches to therapeutic development. Drug repurposing, also known as drug repositioning, has emerged as a paradigm-shifting strategy that utilizes already known pharmacological agents to target novel disease indications, thus greatly shortening the

developmental risks, timelines, and costs. In the current precision medicine and data-driven healthcare landscape, repurposing strategies have witnessed an unprecedented surge owing to advances in artificial intelligence (AI), machine learning (ML), bioinformatics, and systems biology.

The COVID-19 pandemic has also underscored the strategic relevance of drug repurposing, as it was demonstrated that existing drugs such as Remdesivir and Dexamethasone could be rapidly assessed for their utility in emerging health threats. Other drugs such as Sildenafil, originally developed for angina, have found novel therapeutic uses in erectile dysfunction and pulmonary hypertension, thus exemplifying the translational utility of repurposing.

With the convergence of computational biology, real-world evidence, and genome-editing tools such as CRISPR-Cas9, drug repurposing has now become a multidisciplinary and technology-driven paradigm shift in pharmaceutical sciences. However, the issues of intellectual property, regulatory frameworks, data quality, and validation frameworks have remained relatively unexplored in most academic discourse.Thus, this manuscript is both timely and important. It proposes to provide a comprehensive review of the methodologies, predictive platforms, validation strategies, clinical applications, and regulatory limitations related to drug repurposing. This will be of immense benefit to researchers, clinicians, and pharmaceutical scientists looking to accelerate innovation in therapeutics.

Advantages Of Drug Repurposing Over Traditional Drug Discovery:

Since from current years, even though funding for developing a new drug has been increasing but the quantity of drugs which get approved remains low. As a result, people shifted their interest in repurposing of drugs because of different factors unlike traditional method to drug discovery, in drug repurposing we can skip the therapeutic exploratory phase of clinical trials leading to decreased expenditure, saving of time and clinical information also readily available at start of research programme so the risk linked to later stages are significantly lower and another key benefit of drug repurposing is that many candidates had already demonstrated acceptable safety in earlier testing, since both approved medications and both preclinical and clinical data exist, there will be faster progress in discovery and development of drugs. [7]

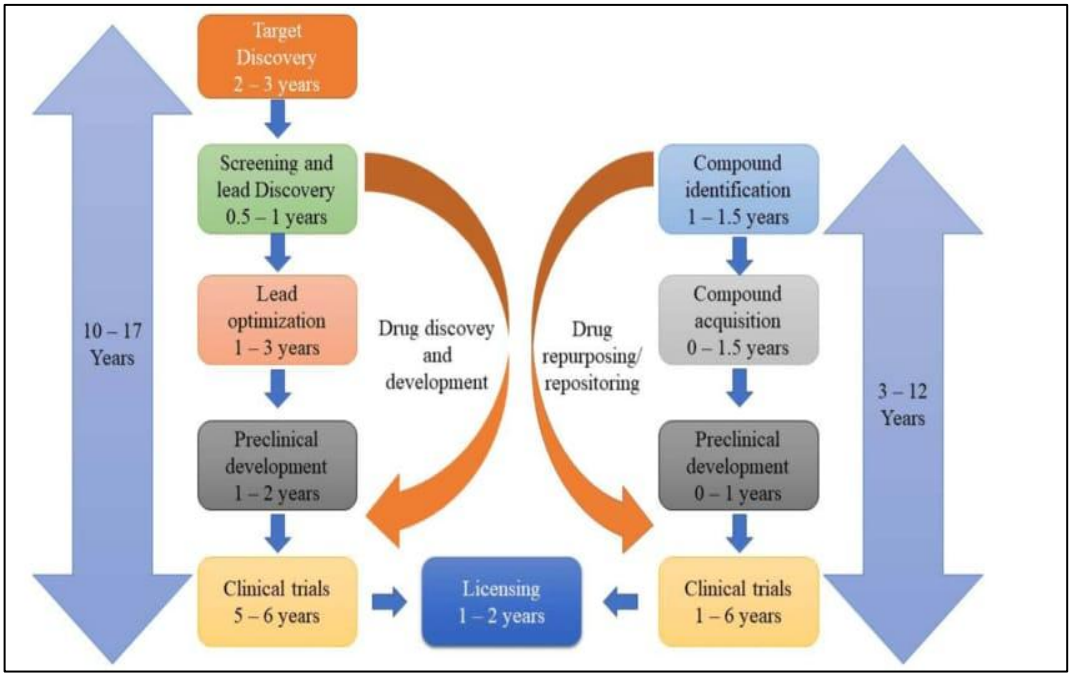

Fig representing Comparison of traditional drug discovery and drug repurposing

Examples Of Drugs That Are Repurposed:

Pembrolizumab was initially used to treat advanced melanoma, but it's also been approved to treat several kinds of cancers and sirolimus was initially indicated for treatment of grafts rejection, but it's also been approved for treatment of condition called lymphangioleiomatosis and suberanilohydroxamic acid was initially indicated to treat lymphoma of skin but it is also repurposed for treatment of cryptogenic fibrosing alveolitis. [10]

DRUGS	ORIGINAL INDICATION	REPURPOSED INDICATION	REFERNCE
Losartan	Antihypertensive agent	Treatment of Alzheimer's disease	[8]
Loxapine	Used to manage symptoms of psychosis symptoms and conditions like schizophrenia	Emotional dysregulation in individuals with autism	[8]
Minoxidil	Used to treat hypertension	Alopecia	[9]
Atomoxetine	Parkinsons disease	Attention deficit hyperactivity disorder	[9]
Raloxifene	Osteoporosis	Breast cancer	[9]

Strategies For Drug Repurposing:

Drug repurposing involves two types of strategies that is off-target and on-target. [11]

- If we look on on-target strategy, the recognized pharmacological action of a drug moiety is leveraged for alternative clinical use. Although the target remained unchanged, the disorder being addressed is different. Examples of drugs that are repurposed by this strategy is minoxidil, this drug has the ability to dilate blood vessels and facilitates activation of potassium channel that leads to increase in frequency of oxygen, nutrients and blood to region of hair follicles thus it can be used to treat alopecia or baldness in males thus being an antihypertensive, minoxidil was repurposed to treat hair loss. [11]

- In off-target strategy, the medications will show their action on previously unexplored biological sites beyond their initial purpose enabling additional clinical applications resulting from molecular targets and therapeutic uses differ from original use. Examples of drugs that are repurposed by this strategy is Aspirin which has been repurposed to treat strokes and heart attacks due to its ability to inhibit coagulation of blood. [11]

Approaches For Drug Repurposing:

Computational Approaches:

Computational approaches frequently identify several promising drug candidates, but the real objective of drug repurposing is to advance just one or two candidates into clinical practice to improve patient outcomes. As a result, lab confirmation of these computational suggested candidates becomes essential. Végner e.t.al conductedan experimental study to validate a previously published Computational repurposing method, demonstrating the effectiveness of the top predictions using COX inhibition tests, ACE inhibition tests, and assays measuring dopaminergic antagonist and agonistic activity. [12]

Network based methods:

Over the past 10 years, network-based strategies have been widely applied for predicting drug responses. These can aid in identifying effective combinations of drug targets, guiding the development of multi drug therapies and enhancing treatment strategies for individual patients with advances in next-generation sequencing, it became feasible to reconstruct cellular and biomolecular networks which naturally form hierarchical structure. Guney e.t.al proposed a proximity metric between drug-disease that evaluates the relationship between drug targets and disease associated genes. This network-level proximity can reveal drugs therapeutic potential and support the discovery of new drug-disease connections. [13] These methods include:

I.Biological network models:

Biological networks are widely employed to describe molecular connections and to model how different biological components interactions. In such networks, edges can represent many types of associations including protein binding, functional similarity among genes because these links capture different biological phenomena networks are often grouped according to type of data they incorporate such as regulatory, metabolic or interaction-based system. Genome-scale metabolic reconstruction built from collections of biochemical reactions, support simulations of metabolic activity and virtual Knockouts that can assist in discovering and prioritizing therapeutic targets. Biological networks can encompass a wide range of molecular relationships including regulatory connections mediated by transcription factors, gene co-expression patterns that reflect group of genes controlled in a coordinated manner. [14]

Network based approaches can be introduced by any of the following three types:

Graph Mining algorithms:

Heterogeneous network clustering: Wu e.t.al employed graph clustering within a Heterogeneous network composed of both diseases and drugs. Information on these entities was obtained from the database called KEGG Medious database and the strength of drug-disease links was assessed using the Jaccard coefficient. Based on shared associated genes similarities between pair of drugs were also quantified using Jaccard Scores. [15]

Graph Mining algorithms also include alogirthms like DrugNet, TP-NRWRH, EMP-SVD. [15]

Matrix completion:

It uses methods like Drug repositioning by Bayesian inductive Matrix completion (DRIMC), NTD-DR to predict drug-disease associations. [15]

Deep learnings:

It includes deepDR, NEDD for predicting drug-disease associations. [15]

Data mining

The vast collections of disease, gene and trug information housed in various databases along with the rapidly expanding body of biomedical, Pharmaceutical and biomedical publications have created a significant demand for data mining that can uncover valuable insights hidden within literature. Most research employing this strategy relies on text mining techniques where this method commonly employed in drug repurposing to locate information linked to specific drug, gene (or) disease and then categorize the identified entities based on their co-occurrence (or) clinical text processing. Workflow in text mining contains four main stages: which includes retrieving relevant data, identifying key entities, extracting meaningful information and uncovering new knowledge. [16]

Machine Learning:

Over the last 20 years, computational drug repurposing has progressed from simple similarity-based strategies (often relying on a single type of biological information) to a sophisticated field that support Machine learning. Like in other domains, Machine learning models in computational drug repurposing depend on large, diverse datasets to learn reliable decision patterns capable of uncovering meaningful relationships among biological entities. The rapid expansion of publicly accessible biomedical data, combined with significant advance in Machine learning across multiple disciplines, has greatly supported development, evaluation and applications of algorithms to identify new drug-disease links and enable drug repurposing efforts. [16]

Structure based repositioning:

Molecular docking is a method used for drug design with the help of structures; thus, it can rapidly assess large chemical libraries. Commercial tools like FLEXY, DOCKTITE, CovDock are used for molecular docking, thus supporting both drug repositioning and drug discovery. Several investigations demonstrate that docking can facilitate drug repositioning. For instance, Shaikh et al, with the help of molecular docking, evaluated 112 anticancer agents against 18 well-established Kinase targets representing 9 tumor types. Multiple modeling suites such as AutoDock Vina, GLIDE, and MOE were employed for comparative assessment. Their findings revealed promising activity for compounds like leucovorin, carfilzomib, epirubicin hydrochloride against several cancer-associated targets. [17]

Experimental Approaches:

Phenotype screening:

A rational drug-discovery strategy that complements target-focused methods and still allows for the kind of serendipity behind many existing therapies is phenotype screening. In general, this involves evaluating candidate molecules in one or more disease models while remaining largely on entirely agonistic of the specific molecular mechanism which may influenced by each compound. Because of this, phenotype screening avoids Knowledge driven bias that can limit target-based approaches. This strategy proved useful in the search for new antimalarial agents where a collection of 2700 approved or investigational compounds was tested for their ability to suppress proliferation of plasmodium falciparum. Even though this method supports early discovery through large

scale, high-throughput evaluation, it focuses on a single therapeutic area and is likely to yield only a small number of active leads. [18]

Genome-wide CRISPR-Cas9 screening:

As an effective tool, it used to enhance target identification while reducing unintended gene modulation, thereby outperforming traditional RNA interference. This CRISPR-based approach enables the identification of precise and highly effective therapeutic candidates which may be new or repurposed, which are directed towards proteomic or genomic targets. By pairing Cas 9 nuclease with a pooled library of guide RNAs, researchers can systematically examine genes implicated in a specific condition. At present this screening method widely used to analyze genes that drive lethality associated traits, helping to nominate targets at both the protein and genetic levels and in turn, highlight existing drugs that may be suitable for repurposing. [19]

Clinical And Real World Based Approaches:

Real world data studies:

Information obtained from sources that include electronic health records, insurance claims, billing systems and registries of patient that are not part of conventional clinical trials is referred to as Real-world data. This data is a useful resource to identify different therapeutic applications for currently available medications (drug repositioning) since it gathers information directly from patients; by using such data, a few numbers of repositioned medications have already been confirmed by several trials. [20, 21]

Methods:

Researchers used various approaches depending on the type of data sources, according to a review of studies utilizing real-world data to find novel medicinal uses. To support repurposing efforts, some relied on a single modal database, such as electronic health records, genetic data, or other real-world datasets, and multimodal databases that integrate numerous data types, including multi-omics resources. [20]

Repositioning with help of single modal database:

To examine this theory, Xu e.t.al. performed a retrospective analysis. After identifying relevant populations and prescription information through automated informatics techniques, such as natural language processing, their study evaluated if metformin may be repositioned for usage in oncology. According to their outcomes, metformin was linked to fewer fatalities following a diagnosis of cancer diagnosis when compared to non-diabetic and diabetic patients who were not taking the medication. Using two enormous datasets from Vanderbilt University Medical Center and the Mayo Clinic, Wu e.t.al. designed an approach for identifying reprofiling signals by assessing how non-oncologic drugs affect survival among people with malignancies. using Vanderbilt data, they found that out of 146 drugs evaluated, 22 medicines belonging to 6 categories were associated with better survival. [20]

Repositioning with help of multimodal database:

To investigate the possible prophylactic effect of levodopa on age-related macular degeneration (AMD), Brilliant et al. combined electronic health records data with insurance claims. According to their previous research, levodopa stimulates GPR143 in the epithelium of retinal pigment indicating that this signaling mechanism may lower the incidence of AMD. According to research, there was a significant delay in the onset of AMD in those who received levodopa compared to those who did not, and there was a substantial negative relationship between exposure to levodopa and the likelihood of getting AMD. [20]

Role Of Artificial Intelligence In Drug Repurposing:

Drug repositioning has recently grown to rely extensively on artificial intelligence. toxicity assessment, Virtual screening, efficacy or dose estimate, repurposing choices, and predicting interactions between chemicals and biological targets are just a few of the steps of medicinal discovery and development that these techniques help. Because it has an immense impact on results, selecting the right AI tool for each endeavor is essential. Repurposing initiatives often employ machine-learning, deep-learning, and knowledge-graph techniques. Because they can analyze drug–target associations, protein–protein interaction networks, uncover new binding sites, and predict protein structures, neural networks and basic artificial intelligence are useful for identifying therapeutic targets. By developing predictive algorithms that can screen vast libraries of compounds, artificial intelligence makes it possible to generate drug repositioning hypotheses in an organized manner. Artificial intelligence can also help to identify promising therapeutic possibilities by revealing correlations between molecules, targets, and disease states through the analysis of large chemical and

biological databases. Furthermore, the development of thorough and methodical repurposing methods is improved by AI's capacity to combine different sources of data. [22, 23]

Challenges And Limitations Associated With Drug Repurposing:

Drug repositioning is a beneficial method, but there are still certain barriers in the way. First, implementing well-known medications necessitates assessing relevant intellectual property, which could make it more difficult to patent repurposed medications. Prices and sales are two more serious issues (Aboy et al., 2022). Availability to standard pharmacovigilance and clinical trial data in medical repositioning has long been restricted by commercial and confidentiality concerns, hindering pharmaceutical companies from embracing this approach due to the absence of patentability, which lowers profit prospects. The lack of accurate and widely used datasets to analyze prediction model accuracy is another barrier to drug repurposing. It becomes difficult to assess various modeling strategies objectively since much research generates their unique evaluation sets, which change from one study to the next. [24,25]

Conclusion:

Drug repurposing has emerged as a important strategy in modern drug discovery, providing a productive substitute for traditional research, which is frequently constrained by exorbitant expenses, protracted schedules, and high failure rates. The methods covered, including computational modeling, phenotypic screening, on-target and off-target tactics, and real-world data analysis, demonstrate how various approaches collaborate to find alternative therapeutic applications for currently available medications. By making it possible to map sophisticated biological networks, integrate multi-omics and clinical information, and forecast drug-disease relationships systematically, advances in artificial intelligence and machine learning have significantly improved the area. These techniques make repurposing more accurate and effective by speeding up the creation of hypotheses, thus enhancing fundamental understanding. Despite its benefits, drug repurposing has significant drawbacks. Broader industry participation is hampered by restrictions on intellectual property and a lack of financial incentives. Translating computational predictions into clinical applications is restricted by inconsistent data quality, a lack of established validation procedures, and complicated regulations. Increased data transparency, uniform evaluation criteria, and cooperation between the regulatory, business, and academic sectors are all necessary to address these problems. Drug repurposing has a very promising future despite these obstacles. Combining AI-driven analytics with experimental validation and expanding real-world evidence will advance precision medicine, enhance therapeutic accessibility, and contribute significantly to meeting unmet clinical needs across diverse disease areas.

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